

patients immediately after the maximal drop in blood pressure. It was given symptomatically, using repeated blood pressure and pulse readings as a criterion of dosage. We attempted to bring the pressure only to its preoperative level. The results were entirely satisfactory. If the dosage by this method is such that no hypertension is produced, we believe very little damage to the patient will result. Slow injection and careful control of physical signs are necessary. The inaccessibility of superficial veins after the patient is draped for operation would suggest, however, the continued prophylactic use of ephedrin before induction of anesthesia. The intravenous administration should probably be reserved for emergencies where insufficient dosage has been previously administered. Accompanying attention to oxygenation of the blood is essential.

We wish to lay stress on the many factors involved in such a complex mechanism as high spinal block. Our brief outline of the major factors involved is probably incomplete. Emphasizing one factor to the exclusion of all others in a given complex tends to mislead those whose scrutiny of a subject is superficial. Detailed experimental data upon which this preliminary report is based will be published elsewhere.

#### CONCLUSIONS

1. Cellular oxygen want per se is one of the prime factors in the circulatory depression accompanying spinal anesthesia.

2. Decrease in the oxygen content and increased  $\text{CO}_2$  content of the blood is present when blood pressure is low in spinal anesthesia.

3. Under high spinal anesthesia with some degree of intercostal paralysis, the circulatory condition is improved when oxygen-rich air is inhaled.

4. The fall of blood pressure in spinal anesthesia tends to be synchronous with and proportional to the amount of intercostal muscle paralysis produced.

5. *Efficient* two-phase artificial respiration will maintain normal blood pressure in presence of cord section at the seventh cervical segment or novocain motor and sensory root paralysis of the whole central nervous system.

6. Under high spinal anesthesia, even when blood pressure has been sustained with ephedrin, there is hypersensitivity to anoxemia. No primary asphyxial rise in systolic pressure occurs.

7. Ephedrin in varying dosage tends to maintain normal blood pressure when administered previous to induction of high spinal block.

8. After the blood pressure drop in high spinal anesthesia, ephedrin is less prompt and less effective if administered other than by intravenous injection.

9. When low blood pressure is present from causes other than spinal paralysis, such as extensive hemorrhage, or prolonged anoxemia, ephedrin may fail to restore blood pressure even when given intravenously.

10. High oxygen content of blood augments the beneficial effect of ephedrin.

11. We have not yet seen evidence of circulatory or other damage from ephedrin if the dose is limited to that sufficient to restore normal blood pressure, provided the tissues are adequately oxygenated.

12. Cord section at the fifth thoracic segment or complete novocain paralysis below this point produces no marked change in blood pressure in the normal dog.

13. With our present knowledge, treatment of accidents following spinal anesthesia should consist of two-phase artificial respiration (preferably with oxygen) plus intravenous ephedrin in such dosage that blood pressure is maintained at the preanesthetic level. Existing fluid deficit should of course be made good.

14. Circulatory depression following high spinal anesthesia with intercostal paralysis is much more marked in animals anesthetized with barbital, ethylene, nitrous oxid, or having morphin-scopolamin as a preoperative sedative, than in the unanesthetized animal.

University of Wisconsin.

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## LEUKOPENIA—A REVIEW: WITH SPECIAL REFERENCE TO AGRANULOCYTIC ANGINA\*

### PART II

By O. H. PERRY PEPPER, M. D.  
Philadelphia, Penn.

**BACTERIOLOGY.**—As might be expected, if the hypothesis of a primary leukopenia and secondary invasion is correct, a number of widely differing bacteriological findings have been reported. Some reports of positive blood cultures have clearly been from instances of overwhelming infection and were not cases of agranulocytic angina. A terminal blood stream invasion, however, may occur in this condition. Cultures from

\* Stanley Black Memorial Lecture delivered at Pasadena, January 12, 1931. Part I in August issue, page 82.

Editor's Note.—The annual Stanley P. Black Memorial Lecture at Pasadena is given in memory of the late Stanley P. Black, a graduate of Northwestern, class of 1887, who came to California in 1897. Doctor Black was professor of pathology in the old College of Medicine of the University of California, was health officer of Pasadena for years, and at all times maintained an active interest in public health work. He had much to do with the Certified Milk Commission of Los Angeles. After his death on February 4, 1921, his friends united in getting up a memorial fund, which sponsors the annual Stanley P. Black Memorial Lecture.

the local lesions probably represent the individual's normal throat or gut flora. It is perhaps noteworthy that *B. pyocyaneus* has been found oftener than might be expected and that it is with this organism that Lovett claims to have produced a closely analogous picture in guinea pigs. Cultures from the bone marrow have not been successful.

As might be anticipated, Vincent's organisms have often been found in the ulcers of the tonsils, pharynx, larynx, and gums. Lesions in these locations are usually rapidly invaded by Vincent's organisms and one should be very cautious in attributing any etiologic significance to their presence. No report of invasion of internal organs or bone marrow by these organisms has come to my attention. In the early days of our knowledge of this syndrome much importance was attributed to the organisms of Vincent, but it is now generally believed that they are secondary invaders, although perhaps important in continuing the process. Buch<sup>12</sup> observed that the Vincent's organisms did not appear in the ulcerations until after several days.

*Predisposing Causes.*—The first reports seemed to limit the disease to women; later an occasional male case was discovered, but all statistics point to a greater prevalence in women (Friedemann,<sup>13</sup> twenty-four women; five men). No age is immune; the records include patients from two weeks to sixty-six years of age. No seasonal incidence has appeared, nor has any geographic influence been observed. The condition is apparently not contagious nor familial.

Many of the cases have been under observation by a physician for a variety of troubles at the time of onset, others in perfect health. Perhaps poor general condition predisposes, but also the syndrome may have been more often recognized when the patient had already been under a doctor's care. Many instances have developed following extraction of a tooth because of peridental infection. This was true in the case of one of our nurses. In other cases, tonsillectomy seems to have precipitated the onset. In a man whom I saw in consultation, puncture of the antrum preceded the onset of the throat ulceration by six days.

*Symptoms.*—In the earlier reports, and even in some recent ones, the statement is made that the onset is always sudden with sore throat or the symptoms of a "cold," high fever and severe prostration. When a blood count was taken the characteristic leukopenia was revealed. Other symptoms due to local ulceration may appear as, for example, dysphagia or pain on defecation. Jaundice is often present. The course was supposed to be progressively downward with death occurring in four to eight days, although it was even then appreciated that a few recovered slowly, only to succumb, it was believed, in a relapse.

It is true that this picture is often seen, but we have learned that many far milder cases occur, and that often an individual may have many attacks of varying degrees of mildness or severity.

*Severe Form.*—In the characteristic severe attack, the patient is highly febrile and may exhibit the early evidences of dehydration. The fever curve is not characteristic; fever, in fact, may be trifling or even absent at first, gradually rising to reach 103 or 104 degrees within a day or two. Occasionally a chill occurs. The prostration is often intense and there may be general malaise. Distinct joint pains have been reported, but my experience does not include this observation. With the higher fever, delirium may appear. This systemic picture is not pathognomonic.

Sore throat or tender gums have been the first local complaint in the vast majority of cases. At first there is only an edema or sponginess, but ulceration and necrosis soon follow. The local pain may be considerable; chewing or swallowing may be agonizing, and the regional lymph nodes become enlarged and painful. The spleen and distant lymph nodes may also enlarge. Within two or three days the necrosis becomes more extensive without corresponding increase of pain.

At the height of the attack the heart rate is increased, the blood pressure lowered and the base of the lungs may be congested. The general picture may resemble that of severe septic infection and death seems to result from toxemia. When improvement occurs, it will show itself by lowered fever, lessened toxicity, and the appearance of granular leukocytes in the blood before any distinct change for the better takes place in the local lesions. These are slow to heal; large necrotic sloughs finally becoming loosened and removable. Bits of necrotic bone may continue to be discharged when the ulcers have involved the alveolus. Convalescence is slow both as to the general strength, the local healing, and the restoration of the white cell count to normal. Remissions and second attacks are common.

*Mild Form.*—As I have said we now recognize the occurrence of attacks far milder than this, and yet in their character justifying our belief that they belong in the same group. A strong argument in favor of this view is the fact that these mild attacks occur as a rule in individuals who have had one or more of the severer forms.

One cannot be sure that all patients who have severe attacks also have mild recurrences. The histories of many fail to reveal any incidents which might be so interpreted, but usually this feature has not been looked for. However, the nurse whose case I have mentioned has not had any recurrences although we have watched for them most carefully. On the other hand, we have a woman in the hospital at this time who has had one or two severe attacks and several mild or abortive ones. These latter have been characterized by a feeling of malaise, a sponginess of the gums, little or no fever, but a distinct drop in the total white count due to disappearance of granular forms.

Her history is interesting. The first proved attack was in March 1930 in our hospital, but her description of a "sore throat" in 1928 and of four similar recurrences in 1929 make me be-

lieve that these were agranulocytic in nature. In her first admission she presented a typical picture in every way except that the blood platelets were reduced as well as the leukocytes. She recovered and left the hospital, after a number of normal white cell counts had been obtained. Twelve days later she was back in another attack; on this visit the lowest total count was 600 with no granular leukocytes seen in a long search. When her local lesions had healed and the count reached 5700 a tooth was extracted without local reaction, but two days later, when we were getting our nerve up to have tonsillectomy performed, the gums became spongy and in five days the total count had fallen to 2800. Operation was postponed and in four days the gums were well and the count 5300. Tonsillectomy has now been performed with a prompt rise in white cells to over 7000, a level never before recorded in her case.

Similarly a male case studied by me in Philadelphia and by Minot in Boston has had many trifling abortive attacks, without distinct local lesions but with a coincident fall in white cell count.

Such evidence as this has very decidedly altered the earlier views and has forced us to start building up a far different concept of the nature of the syndrome. The frequent repetition of attacks of varying severity, commencing with leukopenia and only secondarily and not always progressing to severe systemic reaction and local necroses contradicts the hypothesis that the leukopenia of agranulocytic angina results from an overwhelming anginal infection.

*Recurrent Agranulocytosis.*—Finally a case report by Rutledge, Hansen-Prüss, and W. S. Thayer<sup>14</sup> of Johns Hopkins seems to carry our changing conception of the disease one step further. Their case is reported under the title "Recurrent Agranulocytosis" which is used instead of agranulocytic angina because the basic condition, a cyclic leukopenia, is not always accompanied by angina. Their patient, now a man of twenty years of age, presents, to quote their words, "a remarkable instance of cyclic, agranulocytic angina associated with fever and constitutional symptoms but without anemia, beginning at the age of two and one-half months, and recurring at intervals of approximately three weeks during the entire life of a man twenty years of age."

This very remarkable case is unique, but two of the patients whom I have seen, on being carefully questioned described what might have been repeated earlier milder attacks. Probably similar cases will be discovered.

#### COMMENT

As a result of our growing body of experience, I think you will agree that certain statements about agranulocytic angina seem justified:

1. The evidence is sufficient for us to conclude that the leukopenia precedes the ulceration, fever, or other systemic manifestations.

2. This leukopenia is not merely a manifestation of one of the well-recognized causes of

leukopenia such as that following arsphenamin, or that occurring in overwhelming sepsis.

3. The angina and other ulcerations are secondary and merely represent the invasion by an opportunist flora of a poorly defended body border. Such ulcerations do not always occur. These assumptions explain the nonspecificity of the flora, and the likelihood of local invasion by Vincent's organism. Possibly the ulcerations once established tend to prolong and intensify the leukopenia.

4. For the present, we must group together cases and attacks of very varying severity; at the one end of the scale such a case as that reported from Johns Hopkins and at the other end, fulminant cases dying in what appears to be a first attack.

5. No cause for the apparently spontaneous leukopenia has been discovered. It must be such as to permit of its periodic action over a prolonged period of otherwise normal health.

6. It seems theoretically likely that those attacks which are apparently precipitated by a mucous membrane trauma have occurred in an individual subject to periodic leukopenia and happening to be in such a period at the time of the exciting incident.

In other words, angina may occur spontaneously or following mucous membrane trauma during any period of leukopenia. There is nothing, however, about such a leukopenic angina to suggest the cause of the leukopenia. In some instances a recognized cause of leukopenia is lacking and we are forced to employ some such term as idiopathic leukopenia; some of these exhibit a cyclical or periodic tendency. Leukopenia of this type when accompanied by angina and systemic reactions forms the syndrome entitled agranulocytic angina.

Such a concept finds a startling analogy in purpura hemorrhagica. Here also is a failure of one function of the bone marrow—sometimes the platelet forming function, secondary to a clearly recognized cause, sometimes forming one part of the triad of aplastic anemia, but in still other instances continuing throughout a patient's life with, however, only intermittent purpura. The further one carries this analogy the more parallel the evidence seems to be.

We lack altogether any knowledge of the cause which produces recurrent agranulocytosis. What is the unknown factor, the x, in these patients which renders them liable to spontaneous agranulocytic angina, which makes it dangerous for them to have a dental extraction, and which perhaps makes them more likely to develop dangerous leukopenia after such an incident as an injection of arsphenamin?

Studying the cases I have seen for some common factor which might be the unknown x of our problem, I have been struck by the presence of allergy in each. This may, of course, be a mere coincidence, but this is unlikely for allergy occurs in only 10 per cent of the race. I fully realize that we are in a period when it is the fashion to explain everything upon an allergic basis; diges-

tive troubles, migraine, epilepsy, and many others have recently been added to the list of allergic conditions. And yet I am sufficiently impressed by the evidence to suggest that agranulocytic angina may have allergy as the background—not of the angina directly, but of the leukopenia which permits the angina. The hypothesis which forms in my mind would relate the recurrence of leukopenia to that seen upon the entrance of a foreign protein into the body.

That there is a rhythm of the total white cell count has been known for years; Türk believed the daily low point came early in the morning with a drop to about 5000 due to a reduced number of neutrophils. Sabin<sup>15</sup> and her colleagues found that the daily variation of the white count was such that the highest count was usually twice the lowest.

In recurrent leukopenia we have a periodic or occasional excessive lowering of the leukocytes under some influence which might conceivably be allergic. The literature contains no supporting evidence for this hypothesis. Kopelowitz<sup>16</sup> does suggest that there must be a factor, some idiosyncrasy or allergy, or possibly endocrine factor that renders the hematopoietic system susceptible to a noxious agent. He does not report any evidence to support his view.

The first case in which the presence of allergy was brought to my attention was one which will be reported by Dr. Mackinnon Ellis. The allergic state came out clearly in her history, but only after our interest was attracted by a violent urticaria which followed upon a transfusion from a donor who had recently eaten of a food to which the patient was sensitive. It is further interesting that the white count, which had been rising, fell back sharply to a very low figure following this reaction.

Another patient has hay fever and migraine which has been attributed to food allergy. Another was proved food sensitive.

Dr. Joseph M. Hayman, Jr., of the Lakeside Hospital, Cleveland, knowing of my interest in this hypothesis, has sent me a most interesting record of a woman who had entered the hospital on several occasions because of severe asthma. She was sensitive to a number of foods and always had an eosinophilia. She underwent an attack of fever, red spongy gums, and severe leukopenia. Urticaria followed transfusion in her case also. Eosinophilia was present in Thayer's case.

This evidence is, of course, far from sufficient for any dogmatic claims, but it is certainly suggestive and the hypothesis seems tenable. We know of a leukopenia from foreign protein, we know of other allergic manifestations which at times are periodic and recurrent. The best we can do at present is to watch for further evidence.

#### TREATMENT

*Treatment of the Angina.*—The treatment of agranulocytic angina has varied somewhat, according to the views held concerning the nature of the condition. The earlier reports all record efforts directed at lessening the infection both

locally in the ulcerations, and systemically when a blood stream infection was present or suspected. Arsphenamin has been very widely administered without any apparent beneficial result. It is certainly unwise to employ an agent which is in itself a cause of leukopenia. The use of arsphenamin has arisen from a belief that the Vincent's organisms found in anginal lesions were important and required treatment.

Undoubtedly the local lesions require attention, but I doubt if it matters so much what measures are used so long as sloughs are cleaned away and the parts cleansed at frequent intervals. Perhaps the local use of arsphenamin is justifiable, and Babbitt<sup>17</sup> is enthusiastic over the results with 25 per cent trichloroacetic acid and 10 per cent neoarsphenamin in glycerin.

*Treatment of the Leukopenia.*—Where the cause of a leukopenia is known it must be removed if possible and repeated transfusions employed to tide over the interval until the patient's bone marrow is given a chance to reassume its function. Where the cause is not known, as in agranulocytic angina, transfusion seems to offer the best hope. It may be argued that the number of leukocytes supplied is too small to be very helpful. It is true that mathematically the effect on the total count of the patient is not striking. A transfusion of 500 cubic centimeters of blood with 8000 white cells per cubic millimeter only contains 400,000,000 leukocytes which are rapidly distributed and perhaps destroyed throughout the host's circulation and tissues. In one very severe attack not a single granular leukocyte was seen in spite of transfusions sufficient to supply 2000 per cubic millimeter of the patient's blood. Nevertheless such transfusions can be repeated, if necessary, daily, and I believe do accomplish good. They should be large transfusions, given daily, from donors who have been carefully typed and also who have fasted for a number of hours. Plethora, unless extreme, is no contraindication; when plethora is marked, venesection may precede the transfusion.

No satisfactory method of transfusing leukocytes alone has come to my attention, nor any beneficial results from any leukocytic extract.

Even if the leukocytes of a transfusion are destroyed, it is possible that the products from their death form the normal and perhaps most potent stimulus to the bone marrow for the production of new cells. In the final analysis it is a resumption of leukocyte formation which must occur if the patient is to recover. If transfusions should help to bring this about, even indirectly, they would be more valuable than supplying a few cells to function during the necessarily short period.

An argument used against transfusion in anemia is sometimes applied here, that by supplying the lacking elements the bone marrow loses some of the keen stimulus to resume its activity. A good example of this point of view is offered by Minot's treating a case of agranulocytic angina by free bleeding, hoping thus to stimulate the bone marrow. The patient recovered. Our pa-

tient who did so well after tonsillectomy had quite a severe hemorrhage a few hours after returning to the ward; possibly it was the hemorrhage rather than the removal of the tonsils which raised her leukocyte count.

The various liver extracts seem useless, and no chemical has any specific effect. On the theory that while heavy exposures of x-ray depress the bone marrow, small doses are stimulating, Friedemann reported using minimal radiation of the long bones with miraculously prompt benefit. A later report by Friedemann and Elkeles<sup>18</sup> does not sound so optimistic, nor has the treatment been favorably reported upon by others, although tried in many cases. Of the four patients on whom I have seen it tried, none experienced the prompt feeling of well-being nor did young granular cells appear in the blood, as it has been claimed.

We must learn the underlying cause of the leukopenia which is the basis of so-called agranulocytic angina, in order that treatment may be directed not only at the local ulcerations, at the need of circulating leukocytes and at the dormant marrow, but also at this underlying cause whether it prove to be allergy or some still unsuspected factor.

550 Maloney Pavillion, University of Pennsylvania Hospital.

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## THE MENTAL HYGIENE SURVEY OF CALIFORNIA\*

### PART I

By FREDERICK H. ALLEN, M. D.

Philadelphia

AND

GLENN MYERS, M. D.

Los Angeles

LONG ago mental disorders were regarded with the same misunderstanding that gave rise to myths. Eventually came the recognition of the major psychotic disorders as medical problems. Until the twentieth century, however, medical principles were applied almost solely to the more apparent adult psychotic and psychoneurotic disorders. Then came the knowledge that these disorders are the outgrowth of conditions existent in the childhood of the subjects and might have been prevented had proper approach been made. Preventive mental endeavor so became concentrated in the child rather than in the adult. Now

it is further recognized that mental hygiene work cannot be complete without combined work with the child, the persons with whom the child comes into contact and the other environmental factors. Treatment of the child (or of the adult) cannot be detached from a total situation involving home, parents, brothers and sisters, school, neighborhood and companions. Psychotherapy must be applied to persons and psychiatric social therapy to situations.

#### MENTAL HYGIENE PROBLEMS CONFRONT ALL PHYSICIANS

Every practitioner of medicine, no matter what his specialty, is confronted with a great number of mental hygiene problems. His ability to meet such problems depends upon his understanding of them through education and practical experience. His education usually has been wholly inadequate ("only seventeen of the sixty-four four-year medical schools in the United States require of their students as much as one hundred hours of psychiatric study"<sup>1</sup>) and he is prone to develop erroneous concepts through unguided experience. Understanding of the psychotic or psychoneurotic adult cannot be complete without understanding of the child and the situational influences that tend to the development of deviations from the normal personality. Such understanding is to be had only through special work with children such as, for example, has been developed in child-guidance clinics with the characteristic personnel set-up centered around psychiatrist, psychologist, and psychiatric social worker. Professional education is thus of utmost importance, in order that the medical practitioner not only shall treat his patients wisely but that he shall disseminate practical information and advice to the public personally or through writing. Similar education is needed by public health officers, nurses, social workers, teachers, administrators, recreation directors, policemen, probation officers, judges and practicing lawyers. Constructive education is the backbone of the mental hygiene approach.

#### UNITED STATES STATISTICS ON HOSPITALS FOR THE MENTALLY ILL

Mental health has been defined as "the adjustment of individuals to themselves and to the world at large with a maximum of effectiveness, satisfactions, cheerfulness and socially considerate behavior, and the ability to face and accept the realities of life."<sup>2</sup> Obviously the field of mental hygiene is a vast one. In federal, state, county, city, and other hospitals for nervous and mental patients in the United States, there was in the year 1930 an average daily census of 415,042 patients, representing a net increase over the year 1929 of 19,635. In total capacity, the 561 nervous and mental hospitals exceeded the 4302 general hospitals by 66,310 beds.<sup>1</sup> It has been found that there are, in mental hospitals, 250 patients over fifteen years of age for every 100,000 of the general population; 80 (per 100,000 population) are admitted each year, 70 of these for the first time. It has been estimated that "the

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Editor's Note.—See, also, a preliminary report on the California State Mental Hygiene Survey in December 1930 California and Western Medicine, page 872.